COMMENTARY

General and Specific Inheritance of Substance Abuse and Alcoholism

DRUG ABUSE and dependence are prevalent behaviors that are pernicious in their effects on individuals, families, and communities. However, while it is true that many addictive drugs have the ability to consistently elicit common neurochemical responses, a critical observation is that individuals are differentially vulnerable to addiction. The origins of differential vulnerability are either innate (genetic) differences in neurochemistry and behavior, environmental differences, or a combination of both. In Western cultures, we have attempted to prevent and reverse the course of addictions using interventions based in both moral and biomedical frameworks. An addiction is a bad choice (sin) to be chastised and it is also an affliction (disease) to be treated. The fact that we have failed too often with either approach suggests that a better understanding of the origins of addiction could be useful, to help people make better decisions and to improve the basis of intervention.

See also pages 967, 973, and 982

In this issue are 3 articles on inheritance and familiality of addictions.[1-3] The convergent data in these studies are from 2 distinctly different sources: the Vietnam Era Twin Registry[1] and families of drug abuser probands and alcoholic probands.[2,3] The Vietnam-era twin sample is the only population-based study of the 3 and the only twin study. Twin studies have unique power to more precisely define the influence of genetic and nongenetic factors in the etiology of disease. This particular twin sample reveals similar overall patterns of pathology as reported in the National Comorbidity Survey in the same age group.[4] Of 5150 potential pairs, 3372 were successfully interviewed—a very large twin sample and an impressive completion rate owing to an individual subject completion rate of 80%. Moreover, if there is a bias in ascertainment of twins, the result would likely be underascertainment of jointly affected twin pairs, leading to lower heritability estimates. The 2 family-based studies evaluate shared and individual liability for different addictions in relatives of clinically ascertained drug addicts and alcoholics. Thus, the results of these studies are applicable both to clinical populations and to the general population.

The new results reported here and in the 1996 article by Tsuang et al[5] firmly establish addictions as genetically influenced complex disorders and add new information on what these disorders have in common. The drug addictions join a series of other conditions—for example, lung cancer, cardiovascular disease, acquired immunodeficiency syndrome, and alcoholism—that are recognized as common, complex, genetically influenced diseases. Each of these disorders can be profoundly influenced both by inherited genes (for example, *CYP2D6* and *GSTM1*, *APOE* and *APOB1*, *CCR2* and *CCR5*, and *ADH2* and *ALDH2*, respectively) and by life choices (for example, smoking, diet and exercise, condom use, and abstinence from alcohol, respectively). Owing to the heterogeneity of influences, the contribution of genotype and environment in any particular individual is unknown, even if after a lifetime we know whether they have manifested the disease. Genes will generally be observed to act probabilistically rather than deterministically. Thus, individuals with the same genotype (identical twins) will frequently be discordant for the disease.

Individuals who abuse any one category of drugs are likely to abuse drugs in other categories. These studies define the relative contributions of gene and environment to this comorbidity. The prediction that emerges is that the genes that should eventually be identified are likely to act in both drug-specific fashion (for example, the alcohol metabolic gene, *ALDH2*) and in general fashion (for example, the serotonin transporter gene, which has been proposed to affect personality). Likewise, drug-specific (such as availability) and general (such as poverty) environmental factors wi be found.[6]

Tsuang et al[1] showed both general (common to 5 classes of drugs) and drug-specific genetic and environmental vulnerabilities to drug addiction. Model fitting for the common vulnerability model gave variance components of 31%, 25%, and 44% for the additive genetic, family environment, and specific environment factors, respectively. However, the importance of drug-specific genetic and environmental factors varied widely for specific drugs. For marijuana, stimulants, and sedative drugs, the proportion of the total variance due to both drug-specific genetic and environmental factors was 30%, but for psychedelics it was less (15%), and for opiates it was highest (50%). The

This article is also available on our Web Site: www.ama-assn.org/psych.

drug-specific genetic variation was estimated to be one third or less of the total genetic variance for marijuana, stimulants, and sedatives, but the heroin-specific genetic variance was 70%. Psychedelics showed no drug-specific genetic factor. Drug-specific family environmental variance was nonzero only for one drug (marijuana) while for other drugs the drug-specific nonfamily environmental factors contributed about one third of the total nonfamily environmental variance. Thus, these analyses point to both general and drug-specific genetic and environmental factors in substance abuse, where psychedelics have the least and opiates the most drug-specific factors.

The existence of both general and specific vulnerabilities to substance disorders is also borne out in the family studies. Evidence for general vulnerability is seen in the nicotine drug disorder data of Bierut et al[3]; the proportion of relatives with nicotine abuse ranges from 60% to 78% in relatives of probands with various drug disorders as compared with 44% in relatives of controls. Merikangas et al[2] found overlap in the within-drug vs cross-drug vulnerabilities of relatives. However, as in Bierut et al, the odds ratios were highest for recurrence of the same drug disorder in relatives of the proband (with drug-specific relative risks of 10.2 for opioids, 4.4 for cocaine, and 5.8 for marijuana) as compared with cross-drug associations. In the study by Bierut et al, detailed information on alcohol together with marijuana, cocaine, and tobacco use in probands and families enabled the strong conclusion that the drug-specific relative risk for each of these was about 1.7 to 1.8 and was, at least in part, independent of transmission of alcoholism. In addition, both family studies support the importance of genetic factors in alcoholism: about half of the brothers and one quarter of the sisters of alcoholic subjects had alcoholism.[3] However, neither family study supports an independent influence of comorbid substance abuse on the risk of alcoholism in relatives of alcoholic probands. The rates of alcoholism in siblings of alcoholic probands are similar[3] or less[2] than rates in siblings of probands who have both alcoholism and substance abuse. In the families studied by Merikangas et al,[2] rates of alcoholism were increased in relatives of alcohol- and cannabis-dependent subjects but were not actually increased in the relatives of opioid- or cocaine-dependent probands. In the symmetrical alcoholic proband with relative comparison, the risk of developing marijuana, cocaine, or nicotine dependence was influenced by the proband's alcoholism but the vulnerability was also in part independent and substance-specific for each substance (marijuana, cocaine, and nicotine).[3] The overall conclusion that drug dependence in probands is nonpredictive of alcoholism in relatives is provocative and strongly implies that specific genetic factors are involved in alcoholism. Again, Kendler et al,[7] parental history of drug abuse or alcoholism was nonpredictive of the other disorder in offspring. All of these new findings in large (N=1627 and N=4449) and carefully characterized data sets are consistent with previous studies on the familial transmission of alcoholism and other substance abuse (see Kendler[7] et al and reviews in Bierut et al[3] and Merikangas et al[2]). Taken together, these findings confirm that a general vulnerability factor is insufficient to explain the role of genotype in substance abuse and alcoholism. Studies to identify genes in these disorders should be designed to identify both the general and drug-specific genetic factors.

The role of genetic factors in substance abuse will ultimately be understood in particular environmental contexts. For example, the protective effect of the *ALDH2-2* allele in alcoholism remains visible in Asians who have immigrated to North America, but prevalence of alcoholism is higher in the North American milieu, where more alcohol is consumed.[8] It is notable that Bierut et al found that birth cohort, sex, and other substance dependence were stronger predictors of vulnerability than relationship to a proband.

The heritability of the addictions is substantial; the role of genotype accounts for about one third of the overall variance in liability.[1,5] As for calculations of relative risk in families of probands, for example the 8-fold elevated risk observed by Merikangas et al[2] or the 2-fold relative risk seen by Bierut et al,[3] these ratios will be largely determined by population base rates and our ability to estimate them. However, the strong implication of these results is that it would be worthwhile to identify genes for addiction. These studies showing the existence of both shared and unique factors in addictions clarify how this goal should be accomplished.

David Goldman, MD
Andrew Bergen, PhD
Laboratory of Neurogenetics
National Institute on Alcohol Abuse and Alcoholism
12420 Park Lawn Dr, Room 451
Rockville, MD 20852

REFERENCES

1. Tsuang MT, Lyons MJ, Meyer JM, Doyle T, Eisen SA, Goldberg J, True W, Lin N, Toomey R, Eaves L. Co-occurrence of abuse of different drugs in men: the role of drug-specific and shared vulnerabilities. *Arch Gen Psychiatry*. 1998;55:967-972.
2. Merikangas KR, Stolar M, Stevens DE, Goulet J, Preisig MA, Fenton B, Zhang H, O'Malley SS, Rounsaville BJ. Familial transmission of substance use disorders. *Arch Gen Psychiatry*. 1998;55:973-979.
3. Bierut LJ, Dinwiddie SH, Begleiter H, Crowe RR, Hesselbrock V, Nurnberger JI, Porjesz B, Schuckit MA, Reich T. Familial transmission of substance dependence: alcohol, marijuana, cocaine, and habitual smoking: a report from the Collaborative Study on the Genetics of Alcoholism. *Arch Gen Psychiatry*. 1998;55:982-988.
4. Anthony JC, Warner LA, Kessler RC. Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: basic findings from the National Comorbidity Survey. *Exp Clin Psychopharmacol*. 1994;2:244-268.
5. Tsuang MT, Lyons MJ, Meyer JM, Doyle T, Eisen SA, Goldberg J, True W, Lin N, Toomey R, Eaves L. Genetic influences on *DSM-III-R* drug abuse and dependence: a study of 3372 twin pairs. *Am J Med Genet Neuropsychol Genet*. 1996;67:473-477.
6. Crum RM, Lillie-Blanton M, Anthony JC. Neighborhod environment and opportunity to use cocaine and other drugs in late childhood and early adolescence. *Drug Alcohol Depend*. 1996;43:155-161.
7. Kendler KS, Davis CG, Kessler RC. The familial aggregation of common psychiatric and substance use disorders in the National Comorbidity Survey: a family history study. *Br J Psychiatry*. 1997;170:541-548.
8. Tu GC, Israel Y. Alcohol consumption by orientals in North America is predicted largely by a single gene. *Behav Genet*. 1995;25:59-65.